REMARKS

Upon entry of the amendments submitted herewith, claims 18-23 and 25-67 will be pending in this application. Applicants respectfully submit that the claim amendments submitted herewith do not add any new matter within the meaning of 35 U.S.C. §132 to the application.

Accordingly, entry of the above amendments is respectfully requested.

1. Rejection of claim 67 under 35 U.S.C. §112, 2nd paragraph

The Official Action states that claim 67 is rejected under 35 U.S.C. §112, 2nd paragraph as being indefinite for allegedly reciting a tradename, "Polyvidone K90". The Examiner suggests replacing the name with a generic name for the polyvinylpyrrolidone.

RESPONSE

Regarding the rejection of claim 67, applicants respectfully point out to the Examiner that claim 67 has been amended to recite a generic name for the polyvinylpyrrolidone and its known molecular weight. Thus, the basis for this rejection is moot.

Applicants also note that claims 33-35 have also been amended to replace the term "Polyvidone K90" with the same amendment.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this rejection.

2. Rejection of Claims 18-23, 25-32, 36, 37, and 58-67 under 35 U.S.C. §103(a)

The Official Action states that claims 18-23, 25-32, 36, 37, and 58-67 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Rennard, et al. (US Published Application No. 20030018071) in combination with Ghebre-Sellassie et al. (US Patent No. 6,667,362) and Thakkar (U.S. Patent No. 4,024,240).

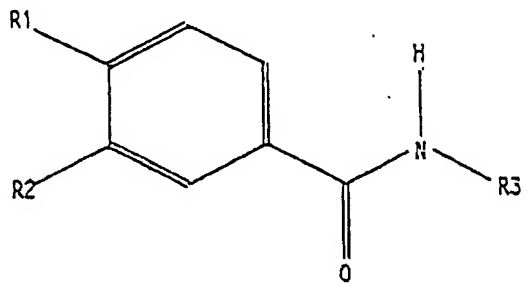
RESPONSE

Applicants respectfully traverse this rejection. The cited references do not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The Examiner has failed to establish a *prima facie* case of obviousness against the presently rejected claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Applicants note that claim 18 is drawn to a solid dosage form in tablet or pellet form for oral administration of a PDE 4 inhibitor, comprising a PDE 4 inhibitor together with polyvinylpyrrolidone as binder, and one or more other suitable pharmaceutical excipients, wherein the PDE 4 inhibitor is a compound of the formula I



(I)

in which

R1 is difluoromethoxy,

R2 is cyclopropylmethoxy and

R3 is 3,5-dichloropyrid-4-yl,

or a salt of this compound, an N-oxide of the pyridine of this compound or a salt thereof,

wherein said dosage form has immediate release of the PDE 4 inhibitor, and wherein the polyvinylpyrrolidone is selected from the group consisting of polyvinylpyrrolidone of molecular weight 28,000 - 34,000, polyvinylpyrrolidone of molecular weight 44,000 - 54,000 and polyvinylpyrrolidone of molecular weight 1,000,000 - 1,500,000.

As has been discussed with the Examiner in previous conversations and in the in-person interview of November 29, 2005, the scope of claim 18 is not rendered obvious by the cited Rennard et al. and Ghebre-Sellassie et al. references because there is no motivation to combine the teachings of Rennard and Ghebre-Sellassie et al. The additional combination with Thakkar does not correct this deficiency.

The Examiner states in the Official Action that

> it would be prima facie obvious...at the time of the invention to add polyvinylpyrrolidone to the formulations of Rennard. The motivation to do so comes from the '362 patent which suggests this modification in order to increase the bioavailability of the drug. Although Rennard does not teach the molecular weights recited in instant claims, Thakkar notes that the range of polyvinylpyrrolidone molecular weights recognized as useful in pharmaceutical dosage forms includes all of the claimed polyvinylpyrrolidones. As such, it would be merely a matter of routine experimentation or optimization to find which polyvinylpyrrolidone achieved the best result.

Applicants respectfully disagree with the Examiner's position as follows.

The primary Rennard et al. reference teaches the combination of certain PDE4 inhibitors with a pharmaceutical carrier. The Rennard et al. reference does not teach each and every element of the presently pending claims. In particular, it neither teaches compositions containing PVP in any amount, nor specific molecular weight ranges for the PVP as presently claimed. Further, the Rennard et al. reference does not discuss the solubility of drugs. Further, Rennard et al. do not recognize the need for an immediate release dosage form containing polyvinylpyrrolidone (PVP) because they already teach an "immediate release" tablet in Example 4 at Table 2 which does not contain PVP. Accordingly, the cited art does not provide motivation to obtain an "immediate release" tablet by combining the embodied disclosure with any other reference, since Rennard already teaches an "immediate release" tablet.

The secondary Ghebre-Sellassie, et al. reference merely states that compositions comprising a carrier polymer such as PVP, "increase the bioavailability of various water insoluble drugs by increasing their dissolution rates..." (See col. 2, line 67 - col. 3, line 1). No degree of dissolution increase is provided in the cited art of record. No comparative data is provided in the cited art of record. As such, the cited art of record is simply an

invitation to experiment to determine which types of PVP are useful to provide an acceptable dissolution profile.

In addition, Ghebre-Sellassie requires the addition of a unique third component, a plasticizer/solubilizer, in addition to the antibiotic and PVP, in order to attain an increased dissolution rate. See col. 3, line 64, to col. 4, line 8, and claim 1 at col. 6, lines 2-6. As such, Ghebre-Sellassie appears to suggest that the form of PVP is not critical, but its combination with a required plasticizer/solubilizer is the critical element. Accordingly, the cited art of record is also simply an invitation to experiment to determine which types of plasticizers/solubilizers in combination with PVP are useful to provide an acceptable dissolution profile.

The Thakkar reference teaches antibiotic compositions which contain PVP having a molecular weight in a broad range of 10,000 - 360,000. Thakkar discloses at col. 4, lines 54-58 that "although the molecular weight of the PVP is not a critical feature of the dispersions of this invention, especially-preferred dispersions are those prepared with a PVP having a molecular weight in the range of about 10,000 to about 60,000." (emphasis added) Thus, the Thakkar reference does not recognize the importance that the molecular weight of the PVP has on a dissolution profile of a particular drug.

Further, applicants again point to the data in the

specification at page 20 and in Figure 1. The data shows that the instantly claimed dosage forms comprising roflumilast and PVP lead to higher serum levels of roflumilast in the blood more quickly than the dosage forms comprising roflumilast and no PVP.

Moreover, in the specification at page 11, applicants describe that "[i]t has surprisingly been found that dosage forms of the invention … have similar advantageous properties in relation to the bioavailability of the PDE 4 inhibitor whose solubility is slight as do dosage forms produced by first producing solid solutions of PVP and PDE 4 inhibitor." Thus, at the time of invention, there was no reasonable expectation that one of ordinary skill in the art reading the cited references would have successfully identified that the combination of PVP with a PDE 4 inhibitor would achieve the surprising and advantageous properties discovered by the Applicants. Furthermore, routine experimentation would not have identified these surprising and advantageous properties of the inventive subject matter discovered by the Applicants

Accordingly, the art cited by the Examiner: 1) does not disclose each and every element of the presently claimed invention; 2) Even if the cited art did independently teach each and every element of the presently pending claims, there is absolutely no motivation to combine the Rennard and Ghebre-Sellassie et al. references since Rennard did not recognize the need for an immediate release formulation containing PVP; 3) the Ghebre-

Sellassie et al. reference is an invitation to experiment with different PVP molecular weights; and 4) the Thakkar reference does not recognize the impact that the molecular weight of a particular PVP has on the dissolution profile of a particular drug.

Furthermore, presented herewith, in the accompanying declaration under 1.132 and Appendix, is a compilation of methods and data gathered during studies in the declarant's laboratory of: 1) the solubility for physical mixtures and various solid dispersions of pure roflumilast (containing no PVP or carriers) vs. the solubility of roflumilast in formulations containing PVP of a certain molecular weight range; and 2) the dissolution of roflumilast in a tablet formulation containing PVP of a certain molecular weight range vs. the dissolution of roflumilast in a tablet formulation containing other carriers, but no PVP. This declaration and data unequivocally and unexpectedly demonstrates that formulations containing certain molecular weights of PVP have a superior dissolution profile as compared to formulations which contain no PVP, or formulations which contain other carriers, but no PVP. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 18-23 and 25-67 under 35 USC §103(a).

The data in the application and 1.132 declaration is absolutely distinguishable from the cited art, which provides no actual evidence or support that PVP increases dissolution. The

combination of cited references provide no adequate written description or enabling disclosure of PVP increasing dissolution as is described in the present application. The combination of references provides at most an invitation to try to experiment with numerous combinations of PDE 4 inhibitors and known excipients. Such an invitation to try is not the standard for showing a *prima facie* case of obviousness.

If, however, the Examiner insists on maintaining that the presently pending claims are obvious in view of the deficient teachings of the cited references, applicant again respectfully draws the Examiner's attention to the accompanying declaration under 1.132 and Appendix which unexpectedly demonstrates that a formulation which contains PVP has an unexpectedly higher dissolution rate of roflumilast than a formulation which contains pure roflumilast and no PVP, or a formulation which contains roflumilast and other carriers, but no PVP.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 18-23 and 25-67 under 35 USC §103(a).

4. Rejection of Claims 33-35 and 38-57 under 35 U.S.C. §103(a)

The Official Action states that claims 33-35 and 38-57 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Rennard, et al. (US Published Application No. 20030018071) in

combination with Ghebre-Sellassie et al. (US Patent No. 6,667,362) and Thakkar (U.S. Patent No. 4,024,240) and further in view of Remington: The Science and Practice of Pharmacy, 1995.

RESPONSE

Applicants respectfully traverse this rejection. The references of record do not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The Examiner has failed to establish a *prima facie* case of obviousness against the presently rejected claims.

For the sake of brevity, the arguments set forth above in section 3 are incorporated herewith as they pertain to the teachings of the Rennard et al. and Ghebre-Sellassie et al. references. The additional Remington's reference does not remedy the deficient teachings of the aforementioned references and, thus, cannot establish a *prima facie* case of obviousness against the presently rejected claims.

The Remington's reference does not discuss the solubility of drugs. Further, the Remington's reference does not recognize the need for an immediate release dosage form containing polyvinylpyrrolidone (PVP) as presently claimed.

Thus, a person of ordinary skill would not be motivated, upon reading the Remington's reference, to combine it with the teachings

of the other references to obtain an "immediate release" tablet of a slightly soluble drug comprising corn starch.

Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness against the presently pending claims. Again, if the Examiner insists on maintaining that he has established a *prima facie* case of obviousness against the presently pending claims, the data presented in the specification clearly demonstrates unexpected results which would rebut this alleged *prima facie* case.

As such, applicants respectfully request that the Examiner reconsider and withdraw the rejection.

CONCLUSION

In view of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejection of the claims and to allow pending claims 18-23, and 25-67.

If the Examiner has any questions or wishes to discuss this matter, the Examiner is welcomed to telephone the undersigned attorney.

Respectfully submitted,

NATH & ASSOCIATES PLLC

Date: April 27, 2007

Gary M. Nath
Registration No. 26,965
Joshua B. Goldberg
Registration No. 44,126
Charles D. Niebylski
Registration No. 46,116
Customer No. 34375

THE NATH LAW GROUP, PLLC
112 South West Street
Alexandria, VA 22314
Tel: (703) 548-6284
Fax: (703) 683-8396
JBG/CDN\ROAapr07